Appendix A. Conference discussion

Dr T. Treasure (*London, United Kingdom*): There is a matter we need to be clear about, the difference between a prognostic feature and a predictive feature. A feature may be prognostic in the sense of determining a differential natural history in the disease itself. Patients with good prognostic features will live longer whether you operate on them or not. On the other hand, R0 versus R1 may be predictive of better outcome. I would make that distinction. So I would put it to you that interesting though the results are, and important in avoiding unavailing surgery in patients who are going to die quite soon whatever you do, that you have done an analysis of prognostic factors, which are prognostic irrespective of whether you operate or not. It isn't that you shouldn't use that information but you should be very clear in your own mind exactly what you have found. I admire the study, it's very thorough, and the more we know about this disease, the better we're going to be able to treat it.

Dr Pompeo: Your comments are very important, and, of course, they underline the main limit of this study. I perfectly agree with your considerations. Maybe these factors might better be considered as predictive rather than prognostic factors because the main limit of this study is its retrospective nature. The hope is that in the future these kinds of prognosticators can help to avoid aggressive surgery in patients in whom it is unnecessary.

Dr M. Alam (*Dublin, Ireland*): I have just one quick question. You identified a high level of concentration of COX-2. Do you see a role for highly selective COX-2 inhibitors in the future management or treatment of mesothelioma?

Dr Pompeo: Yes. I think one important result is the association between all these factors. There has already been more than one study emphasizing the possible interdependence of all 3 of these factors in revealing the negative or positive effect on the natural history of solid tumours, and I think we will continue to assess all these factors together.

Dr W. Weder (*Zurich, Switzerland*): I have one question. From the study you have done now and the data, how does this influence your next steps?

Dr Pompeo: It's difficult to answer. One thing might be to assess expression of these factors before surgery and to see in which patients COX-2 is very high and the contrary for the other factors, and then avoid extrapleural pneumonectomy in patients with a predictable poor result, but I think the most important thing is to consider this as a first step to better understand pathophysiologic mechanisms of mesothelioma progression and continue to try to find some new therapeutic agents that will be able to help us with this disease.

Editorial comment

May cyclooxygenase-2 (COX-2), p21 and p27 expression affect prognosis and therapeutic strategy of patients with malignant pleural mesothelioma?

Keywords: Malignant pleural mesothelioma; COX-2; p21; p27

Mineo and colleagues from the Department of Thoracic Surgery of the University of Rome retrospectively investigated the immunohistochemical expression of cyclooxygenase-2 (COX-2), p21 and p27 in a cohort of 77 consecutive mesothelioma patients [1]. The triple-combination of high COX-2 and low p21 and p27 expression was found to be the only independent prognosticator for shorter overall survival for mesothelioma patients in the whole panel of factors analysed (beside stage, histology or therapy).

This kind of research — analysis of different markers for the prognosis of several tumours — recently came under some criticism, finding 'another marker amongst thousands'. In my opinion, it is still important research to be performed, especially in the context of mesothelioma research. Heterogeneous results concerning the outcome of patients with sarcomatoid histology or involved mediastinal lymph nodes after induction chemotherapy followed by surgery cannot be only explained by different patient groups [2—4]. There must be differences in the biological features of mesothelioma patients that are responsible for these differing survival outcomes! Therefore, investigation of markers and correlation with clinical outcome may provide new knowledge regarding the biology of this aggressive tumour. Furthermore, subgroups of patients benefitting from aggressive treatment regimens can be defined.

COX-2 is an inducible enzyme, which catalyses the conversion of arachidonic acid to prostaglandins in response to pro-inflammatory or mitogenic signals; it is overexpressed in many solid tumours; and *in vitro* experiments, by using specific COX-2 inhibitors, have shown that COX-2 may be a potential target for novel cancer therapies [5]. Therefore, this marker is a very promising one as it can be used not only for prognostic reasons but also as a therapeutic target. As mentioned in the discussion, several authors have already confirmed the role of COX-2 as a prognosticator in malignant pleural mesothelioma (MPM) [6,7]. The two cyclin-dependent kinase-inhibitors, p21 and p27, are cell-cycle regulators that are implicated in the regulation of the molecular mechanism of cell division. High expression of p27 was correlated to prolonged overall survival of MPM patients [8,9] but, in the underlying analysis, only the triple combination of all markers independently predicted longer overall survival.

The correlation between the expression of the different markers and several clinico-pathological markers was evaluated; it would have been interesting if the authors had provided additional information about the relationship between the different markers. We have shown that p27 immunostaining correlates in a cohort of 352 patients with the expression of p21 [8]. The same was observed by Baldi and colleagues and, in addition, a negative correlation between COX-2 expression and both p27 and p21 was shown [7].

In Table 1 of Mineo et al.'s paper, univariate analysis of the main clinico-pathological variables is illustrated and shows that out of 27 extrapleural pneumonectomies and 44 pleurectomy/decortications performed, 65 patients

present negative resection margins. In our experience, even the most radical procedure of extrapleural pneumonectomy is, in most of the cases, R1 resection only. For anatomical limits, a clear and wide negative resection margin is, in principle, not possible.

As the authors already stated in their discussion, the patients were not uniformly treated. Some patients underwent surgery alone (biopsy-plus-pleurodesis, pleurectomy—decortication or extrapleural pneumonectomies), whereas others experienced any type of multimodal treatment (adjuvant radiotherapy, adjuvant radio-chemotherapy, neo-adjuvant chemotherapy plus adjuvant radiotherapy). This can be explained by a long retrospective observation period of over 20 years. However, this is a problem we are all confronted with in mesothelioma research. As there is no gold standard or standard treatment for these patients and several approaches have been investigated over the past decades, retrospective analyses are generally performed with heterogeneous patient groups. Nevertheless, the suggestion of the authors that in the presence of the combination, COX-2, less aggressive options might be preferred, has to be taken with caution, because of the relatively small number of patients and the fact that 8% of the patients did not undergo surgery except for pleurodesis. This has to be confirmed in a standardised treated patient group.

Without any doubt, these results do justify further investigation in the direction of COX-2, p21 and p27; however, research has to be continued until these markers can help to make strategical therapy decisions for a certain subgroup of patients or can function as therapeutical target.I am looking forward to forthcoming news!

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